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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/661,366	09/12/2003	Randolf Kerschbaumer	20695C-006400US	6755

44183 7590 08/24/2006

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EXAMINER	
SZPERKA, MICHAEL EDWARD	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 08/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/661,366	KERSCHBAUMER ET AL.	
	Examiner	Art Unit	
	Michael Szperka	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15 and 22-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15 and 22-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/28/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's response and amendment received June 20, 2006 is acknowledged.
Claims 16-21 and 25-27 have been canceled.
Claims 1-15 and 22-24 are pending.

Applicant's election of Group I, claims 1-15 and 22-24, drawn to antibodies and pharmaceutical compositions, in the reply filed on June 20, 2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1-15 and 22-24 are under examination as they read on antibodies that bind to and increase the procoagulant activity of blood factor IXa, as well as pharmaceutical compositions comprising such antibodies.

Information Disclosure Statement

2. Applicant's IDS received June 28, 2004 is acknowledged and has been considered.

Claim Rejections - 35 USC § 101

3. 35 U.S.C. 101 reads as follows:

> **Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.**

4. Claims 1-11 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Specifically, antibodies are products of nature. Amendment of the claims to indicate the hand of man in the claimed invention, possibly through the recitation of isolated or purified antibodies if such language is supported by the instant specification, would obviate this rejection. Note that while antibody

fragments can occur as natural degradation products, recombinant, single chain, humanized and labeled antibodies are not found in nature.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> **The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.**

6. Claims 1-7, 9-15 and 22-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for antibodies that comprise SEQ ID NOs:3-8 in their appropriate structural context (i.e. SEQ ID NOs:6-8 in complementarity determining regions (CDRs) 1-3 of the heavy chain respectively and SEQ ID NOs: 3-5 in CDRs1-3 of the light chain respectively) or that comprise SEQ ID NOs:1 and 2, wherein all of the aforementioned antibodies further comprise the functional properties of binding to factor IXa and increasing the procoagulation activity of factor IXa, does not reasonably provide enablement for antibodies that do not comprise all of the aforesaid structural and functional limitations. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicant has generated a monoclonal antibody designated 224F3 that binds to blood factor IX (FIX) and its activated form, factor IXa (FIXa). When FIXa is bound by 224F3, the procoagulant capability of FIXa is increased as measured by increased conversion of factor X (FX) to factor Xa (FXa, see particularly Example 4). 224F3 has been sequenced, with the variable domains of the antibody heavy and light chains being reported as SEQ ID NO:1 and SEQ ID NO:2 respectively (see figures 6 and 7). CDRs 1-3 of the heavy chain of 224F3 are SEQ ID NOs:6-8 respectively while CDRs 1-3 of the light chain of 224F3 are SEQ ID NOs: 3-5 respectively. Note that a complete antibody variable domain comprises 3 CDR, and as such SEQ ID NOs:6-8 are subsequences of SEQ ID NO:1 while SEQ ID NOs: 3-5 are subsequences of SEQ ID NO:2.

Applicant has claimed a broad genus of antibodies and compositions comprising antibodies wherein the antibodies need only comprise one of the above discussed sequences and increase the procoagulation activity of FIXa. The precise location and number of these sequences in the recited antibodies are not specified. For example, one reasonable embodiment of the genus of antibodies as recited in claim 2 is an antibody that comprises SEQ ID NO:3 for the 3 CDRs of the heavy chain and for the 3 CDRs of the light chain.

It is well established in the art that the formation of an intact antigen-binding site requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three different complementarity determining regions, CDR1, 2 and 3, which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin (Janeway et al., Immunobiology, third edition, 1997, pages 3:7-3:11, see entire selection).

The importance of all 6 CDR sequences for specific antigen binding is underscored by the fact that prior art antibodies exist that comprise one or more of the instant recited sequences, yet bind antigens unrelated to FIX (see attached sequence search notes, WO 98/13067A1, WO 02/081496A2, and WO 02/090566A2). Note that in the absence of a recitation that includes all 6 CDR sequences, the sequences of the non-specified CDRs are essentially random, and it is known in the art that even a single amino acid change in a CDR can abrogate the antigen binding function of an antibody (Rudikoff et al. PNAS USA, 1982, 79:1979-1983, of record as C40 in the IDS received 6/28/04, see entire document, particularly the abstract and the middle of the left column of page 1982). Therefore, changes in CDR sequences have unpredictable effects on antibody function. As such it is clear that antibodies which do not comprise all 6 CDR sequences of 224F3 in their proper spatial relationship are not reasonably expected to bind FIXa and increase its procoagulant activity. Note that recitation of the proper spatial relationship among the CDRs is not currently present.

Therefore, given the breadth of applicant's claimed invention, the teachings of the prior art that all 6 CDR are important for the functional property of antigen specific binding, and the teachings of the prior art that an alteration of even one amino acid in a single CDR can eliminate antigen binding, a skilled artisan would be required to perform an undue amount of unpredictable experimentation to make and use the full breadth of applicant's claimed invention.

7. Claims 1-7, 9-15 and 22-24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Applicant has broadly claimed a genus of antibodies that bind and increase the procoagulation activity of factor IXa and comprise at least one amino acid sequence selected from the group consisting of SEQ ID NOs:1-8. To support this genus, applicant has disclosed sequence information for monoclonal antibody 224F3. Monoclonal antibody 224F3 comprises the antibody heavy and light chains variable domains of SEQ ID NO:1 and SEQ ID NO:2 respectively (see figures 6 and 7) and further comprises SEQ ID NOs:6-8 (complementarity determining regions (CDRs) 1-3 of the heavy chain respectively) and SEQ ID NOs: 3-5 (CDRs 1-3 of the light chain respectively).

The guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, § 1 "Written Description" Requirement make clear that if a claimed genus does not show actual reduction to practice for a representative number of species, then the Requirement may be alternatively met by reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Fri. January 5, 2001, see especially page 1106 column 3).

Watson et al. teach that a typical antibody is a 150 kDa molecule made up of two identical copies of a light chain comprising about 220 amino acids and two identical copies of a heavy chain comprising about 440 amino acids (Molecular Biology of the Gene, 4th edition, see page 840). SEQ ID NOs: 3-8 are all short sequences of between 7 and 16 amino acids in length, while SEQ ID NO:1 is 125 amino acids and SEQ ID NO:2 is 106 amino acids. As such, the sequence structural requirements recited in the claim comprise only a very small percentage of the total sequence structure that comprises a typical antibody molecule.

It is also noted that the claimed genus of antibodies also comprises the functional property of binding to and increasing the procoagulation activity of factor IXa. The specification does not appear to teach that a molecule comprising at least one of the recited sequences possesses the recited functional properties.

In University of California v. Eli Lilly and Co. (CAFC) 43 USPQ2d 1398, the court noted:

> "A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene (in the instant case, a peptide) does, rather than what it is. See Fiers, 984 F.2d at 1169-71, 25 USPQ2d at 1605-06 (discussing Amgen). It is only a definition of a useful result rather than a definition of what achieves that result. Many such genes (peptides) may achieve that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin [e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material."

The court has also noted that "Adequate written description requires a precise definition, such as by structure, formula, chemical name or physical properties, not a mere wish or plan for obtaining the claimed chemical invention." Id. at 1566, 43 USPQ2d at 1404 (quoting Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606). Also see Enzo-Biochem v. Gen-Probe 01-1230 (CAFC 2002).

As discussed above, it does not appear that the recited structural features are

sufficient to provide a precise definition of an antibody molecule that comprises the recited functional properties.

Therefore, it appears that the broad genus of antibodies claimed by applicant lacks adequate written description because the recited structural requirements, in the instant case amino acids sequences, are not representative of the overall structure of the claimed antibody molecule, nor are the recited structural requirements clearly correlated with the recited functional properties. As such a skilled artisan would reasonably conclude that applicant was not in possession of the claimed genus of antibodies at the time the application was filed.

Claim Objections

8. Claim 1 is objected to because the abbreviation FIXa should be indicated immediately following the recitation of Factor IXa in line 2 of the claim, or the recitation of FIXa in line 3 should be replaced with "Factor IXa".

Claim 24 is objected to because of awkward language. The phrase "further comprising Factor IX, Factor IXa, or Factor IX and Factor IXa" appears to be clearer and of equivalent scope as compared to the current claim language.

9. No claims are allowable.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Szperka whose telephone number is 571-272-2934. The examiner can normally be reached on M-F 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Michael Szperka, Ph.D.
Patent Examiner
Technology Center 1600
August 11, 2006

8/19/06

G.R. EWOLDT, PH.D.
PRIMARY EXAMINER

```
RESULT 16
AAE33427
ID   AAE33427 standard; protein; 106 AA.
XX
AC   AAE33427;
XX
DT   02-APR-2003  (first entry)
XX
DE   Murine KS-1/4 antibody de-immunised VK5 protein.
XX
KW   Immunoglobulin; diagnosis; epithelial cell adhesion molecule; EpCAM;
KW   kappa light chain variable region; VK; cancer; gene therapy; murine.
XX
OS   Mus sp.
XX
FH   Key             Location/Qualifiers
FT   Region          1. .23
FT                   /note= "Framework region 1"
FT   Region          24. .33
FT                   /note= "Complementarity determining region 1 (CDR1)"
FT   Region          34. .48
FT                   /note= "Framework region 2"
FT   Region          49. .55
FT                   /note= "Complementarity determining region 2 (CDR2)"
FT   Region          56. .87
FT                   /note= "Framework region 3"
FT   Region          88. .96
FT                   /note= "Complementarity determining region 3 (CDR3)"
FT   Region          97. .106
FT                   /note= "Framework region 4"
XX
PN   WO200290566-A2.
XX
PD   14-NOV-2002.
XX
PF   03-MAY-2002; 2002WO-US013844.
XX
PR   03-MAY-2001; 2001US-0288564P.
XX
PA   (LEXI-) LEXIGEN PHARM CORP.
XX
PI   Gillies SD,  Lo K,  Qian X;
XX
DR   WPI; 2003-111985/10.
XX
PT   New recombinant anti-EpCAM antibody having an amino acid sequence
PT   defining an immunoglobulin light or heavy chain framework region, useful
PT   for the diagnosis, prognosis and treatment of cancer.
XX
PS   Disclosure; Page 64; 82pp; English.
XX
CC   The present invention relates to novel recombinant anti-EpCAM (human
CC   epithelial cell adhesion molecule) antibodies comprising an amino acid
CC   sequence defining an immunoglobulin light or heavy chain framework
CC   region. Sequences of the present invention are useful for the diagnosis,
CC   prognosis and treatment of cancer. They are also used in gene therapy.
CC   The present sequence is murine KS-1/4 antibody kappa light chain variable
CC   region (VK5) de-immunised protein. This sequence is used to illustrate
CC   the method of the invention
XX
SQ   Sequence 106 AA;
```

```
  Query Match             100.0%;  Score 44;  DB 6;  Length 106;
  Best Local Similarity   100.0%;  Pred. No. 0.57;
  Matches   10;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 SASSSVSYML 10
              ||||||||||
Db         24 SASSSVSYML 33
```

SEQ ID# 3

```
RESULT 17
AAW37813
ID   AAW37813 standard; protein; 106 AA.
XX
AC   AAW37813;
XX
DT   25-AUG-1998  (first entry)
XX
DE   Humanized anti-Tac antibody light chain variable region.
XX
KW   Humanized anti-Tac antibody light chain; HAT; variable region; MAb;
KW   monoclonal antibody; acute rejection; renal transplant; T lymphocyte;
KW   interleukin-2 receptor; IL-2; competitive inhibition; B lymphocyte.
XX
OS   Homo sapiens.
XX
PN   WO9813067-A1.
XX
PD   02-APR-1998.
XX
PF   23-SEP-1997;   97WO-US016915.
XX
PR   24-SEP-1996;   96US-0026643P.
XX
PA   (PROT-) PROTEIN DESIGN LABS INC.
PA   (HOFF ) HOFFMANN LA ROCHE INC.
XX
PI   Light S,  Queen C;
XX
DR   WPI; 1998-230426/20.
XX
PT   Prevention of acute rejection following renal transplantation - by using
PT   monoclonal antibody that binds the P55 subunit of human interleukin-2.
XX
PS   Claim 20; Page 31; 18pp; English.
XX
CC   The present sequence represents the variable region of the humanized anti
CC   -Tac (HAT) antibody light chain. The invention provide a method of
CC   preventing acute rejection following renal transplantation. The method
CC   involves administering a chimeric or humanized monoclonal antibody (MAb),
CC   e.g. HAT antibody, that competitively inhibits binding of other humanized
CC   MAb to the p55 subunit of the human interleukin-2 (IL-2) receptor
CC   expressed on T and B lymphocytes. Therefore, the method is claimed to be
CC   useful in preventing acute rejection following transplantation of a solid
CC   organ, such as a kidney or liver
XX
SQ   Sequence 106 AA;

  Query Match             100.0%;  Score 32;  DB 2;  Length 106;
  Best Local Similarity   100.0%;  Pred. No. 37;
  Matches    7;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 TTSNLAS 7
              |||||||
Db         49 TTSNLAS 55
```

SEQ ID#4

RESULT 2
ABJ18551
ID ABJ18551 standard; peptide; 17 AA.
XX
AC ABJ18551;
XX
DT 18-FEB-2003 (first entry)
XX
DE Ganglioside-associated recombinant antibody peptide region #16.
XX
KW Cytostatic; chimeric antibody; monoclonal antibody; ECACC 94113026;
KW N-glycosylated ganglioside; anti-idiotypic monoclonal 1E10; metastatic;
KW breast cancer; melanoma; tumour; lung; digestive; urogenital tract;
KW sarcoma; neuroectodermal.
XX
OS Homo sapiens.
XX
PN WO200281496-A2.
XX
PD 17-OCT-2002.
XX
PF 08-APR-2002; 2002WO-CU000003.
XX
PR 06-APR-2001; 2001CU-00000084.
XX
PA (IMMU-) CENT IMMUNOLOGIA MOLECULAR.
PA (DRIO/) MATEO DE ACOSTA DEL RIO C M.
PA (VALL/) LOMBARDERO VALLADARES J.
PA (NAVA/) ROQUE NAVARRO L T.
PA (REQU/) LOPEZ REQUENA A.
XX
PI Mateo De Acosta Del Rio CM, Lombardero Valladares J;
PI Roque Navarro LT, Lopez Requena A;
XX
DR WPI; 2003-046857/04.
XX
PT New chimeric antibodies, useful for treatment, prevention and diagnosis
PT of tumors that express gangliosides, are derived from monoclonal
PT antibodies P3 or 1E10.
XX
PS Claim 9; Page 22; 31pp; Spanish.
XX
CC The invention relates to a chimeric antibody, derived from a monoclonal
CC antibody, which recognises N-glycosylated gangliosides and is produced by
CC hybridoma ECACC 94113026. The chimeric antibody, and similar antibodies
CC derived from the anti-idiotypic monoclonal 1E10 (recognising P3) are used
CC for treatment, localisation and in vivo identification of breast cancer
CC and melanoma, their metastases and relapses, tumours of lung, digestive
CC and urogenital tracts, and sarcoma and tumours of neuroectodermal origin.
CC This sequence represents a peptide region of an antibody of the invention
XX
SQ Sequence 17 AA;

  Query Match   100.0%; Score 60; DB 6; Length 17;
  Best Local Similarity   100.0%; Pred. No. 0.0037;
  Matches   10; Conservative   0; Mismatches   0; Indels   0; Gaps   0;

Qy   1 WIFPGDGSTK 10
              ||||||||||
Db   1 WIFPGDGSTK 10

SEQ ID #7